Author's response to reviews

Title: Lack of association between Cathepsin D C224T polymorphism and Alzheimer's disease risk: An update meta-analysis

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Author's response to reviews: see over
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**Manuscript title:** Lack of association between Cathepsin D C224T polymorphism and Alzheimer’s disease risk: An update meta-analysis

**Dear editor:**

Thanks a lot for having reviewed our manuscript. We really appreciate reviewers for their positive and constructive comments. Now we have revised the manuscript point-to-point according to the reviewers' comments. Most of the revisions are in the manuscript, meanwhile, the comments as listed below.

**Response to Reviewer1:**

1. Page 3 line 7 an innate not aninnate.

   Thanks for indicating this error. Now, we have changed the “aninnate” to “an innate” in the text.

2. Page 4 line 18 polymorphism is not polymorphismis.

   Thanks for indicating this error. Now, we have changed the “polymorphismis” to “polymorphism is” in the text.

3. Page 7 A web-based program – Tell the readers which program and also the reference.

   I am so sorry to tell you that the internet site of the web-based
program (http://ihg2.helmholtz-muenchen.de/cgibin/hw/hwa1.pl) cannot open now. Therefore we use a goodness-of-fit Chi-square test to assess Hardy-Weinberg Equilibrium for the distribution of the genotypes in the control population and we got the same results.

4. Page 8 line 16 or autopsy not or autopsy.

   Thank you. We have changed the “or autopsy” to “or autopsy” in Page 8 line 16.

5. Page 7, Table 1, and Table 2 inconsistent acronym, i.e. EAOD/LAOD versus EOAD/LOAD.

   I am so sorry for these errors. The acronym for early-onset AD and late-onset AD are EOAD and LOAD. Now we have corrected these errors in Page 7, Table 1, and Table 2

6. Table 1 Numbers were not correct for the counts of EAOD and LAOD cases of Italy descent.

   Thanks. In the Bagnoli study of Italian, it investigated the association between Cathepsin D polymorphism with sporadic and familial Alzheimer’s disease. And only the 66 familial Alzheimer’s disease patients were subdivided into EOAD and LOAD, so the 33/33 of EAOD and LAOD cases was the counts of early-onset and late onset familial Alzheimer’s disease.

7. 2. Give ORs, p values and 95% CIs for all the analytical results throughout
the manuscript. (ex: Page 9 subgroup analyses and APOE e4 stratified analyses).

Thank you for the suggestion. We have added the ORs, p values and 95% CIs for all the analytical results throughout the manuscript.

Response to Reviewer 2:

1. The biggest concern as a reviewer is still in understanding why the stratified results (specifically the Caucasian results) differ from the Schurr study. The authors could bolster this discussion by highlighting exactly which datasets differ between the two studies. It appears the 4 Asian population datasets (as the authors highlight) along with the Albayrak, 2010 study which was not included in Schurr and the Mateo 2002 study which was excluded from the Schurr analysis for HWE. Is the difference between the Schurr result in caucasians and the present result in caucasians simply due to the addition of these two datasets? Given this study and the Schurr study are largely the same in terms of the caucasian samples, it seems essential for the author's to explain why their result differs from that of Schurr in specific rather than general terms.

Thanks. Our present meta-analysis differed from Schurr study in two aspects. First, we added four studies in Asian population and two studies in Caucasian population. Second, we only compared the CT vs. CC model and the dominant CT+TT vs. CC model for nearly half of the eligible studies did not detect the homozygous TT polymorphism. While
Schurr study was only analyzing the allele model and it might bring some deviations. After excluding two studies which deviated from the HWE, no significant associations were found between the CTSD C224T polymorphism and AD risk in the Asian (CT+TT vs. CC: OR = 0.968, 95% CI =0.605–1.548, P = 0.891) and Caucasian (CT+TT vs. CC: OR = 1.165, 95% CI =0.981–1.383, P = 0.081). After excluding Albayrak study and Mateo study, a significant association was found in the dominant CT+TT vs. CC genetic model (OR = 1.201, 95% CI =1.004–1.436, P = 0.045). The main explanation was the inclusion of the Albayrak [39] study. The Albayrak study reported that the CTSD C224T polymorphism increased AD risk in men only which might cause the false-negative result. As no study has clarified gender-specific differences regarding lysosomes or its components and the characteristic lesions in AD, therefore, future study with larger samples to investigate the gender-specific is necessary.

2. As mentioned previously, the author's highlight the trend in APOE carriers (Table 3, p = 0.072) in their discussion, yet fail to report a similar trend in Caucasians when using a dominant model (Table 2, p = 0.082). It would seem more fair in the discussion on page 13 to state: "a trend was present in Caucasians when using a dominant coding (p = 0.082)" similar to the way in which the APOE results are summarized. Even better, the authors could choose not to report either nominal trend in the discussion.
Thank you for the suggestion. The pooled odds were higher in APOEε4 carriers than in non-carriers, but with non-significant. So we did not report the trend in the discussion.

3. Additionally, the author's should report the p-value when they remove the 2 studies that violate HWE, particularly given this was the explanation given by Schurr as to why their results differed from previous meta-analyses.

    Thank you for the suggestion. The pooled odds with 95%CI and the p-value were added in the text both in overall population and Asian/Caucasian after removing the 2 studies that violate HWE.

4. Table 2 appears to have some inconsistencies. It reports 23 studies in the overall analysis (Table 2 row 1 and 2), yet 25 studies are present when stratifying (21 caucasian and 4 asian). The forest plot also shows 25 studies, so presumably this is just a typo in table 2.

    I am so sorry for this error. We have corrected the error in table 2.

5. It also is not clear why all studies do not fall into either LOAD or EOAD. Was this due to a lack of age of onset data for the other 13 datasets?

    Only six studies provided the distribution of alleles and genotypes on age of onset and the other studies did not provide the sufficient data. Therefore, all studies did not fall into LOAD or EOAD.

6. Fix abbreviations throughout (i.e. EOAD and LOAD rather than EAOD and
Thanks. We have checked the abbreviations throughout and corrected the error.

Editorial requirements:

1. Please enlarge the figures uploaded in the submission system.

   Thanks. All the figures were enlarged.

2. Please remove figure images in the main manuscript. The legend and title should be part of the manuscript file, given after the reference list. Please ensure that the order in which your figures are cited is the same as the order in which they are provided.

   Thanks. The figure images have been removed from the main manuscript. The legend and title were given after the reference list. We also checked the order of our figures and all figures are cited in the same order as the order in which they are provided.

3. After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

   We have carefully checked and engaged expertise in English for revision our grammar and believed there was no any error in grammar.
We would like to re-submit this revised manuscript to BMC Neurology, and hope it is acceptable for publication in the journal. Looking forward to hearing from you soon.

Sincerely,

Cuiju Mo, Qiliu Peng, Jingzhe Sui, Jian Wang, Yan Deng, Li Xie, Taijie Li, Yu He,

Xue Qin, Shan Li